ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Tecartus 0.4 – 2 × 10^8 cells dispersion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Tecartus (autologous anti-CD19-transduced CD3+ cells) is a gene therapy medicinal product containing autologous T cells genetically modified *ex vivo* using a retroviral vector encoding an anti-CD19 chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv) linked to CD28 co-stimulatory domain and CD3-zeta signalling domain.

2.2 Qualitative and quantitative composition

Each patient specific single infusion bag contains a dispersion of anti-CD19 CAR T cells in approximately 68 mL for a target dose of 2 x 10^6 anti-CD19 CAR-positive viable T cells/kg body weight (range: 1 x 10^6 – 2 x 10^6 cells/kg), with a maximum of 2 x 10^8 anti-CD19 CAR-positive viable T cells.

Excipient(s) with known effect

This medicinal product contains 300 mg sodium.
Each dose contains 0.05 mL of dimethyl sulfoxide (DMSO) per mL of Tecartus.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for infusion.

A clear to opaque, white to red dispersion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tecartus is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.

4.2 Posology and method of administration

Tecartus must be administered in a qualified treatment centre by a physician with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with Tecartus. At least 1 dose of tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available prior to infusion. The qualified treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose.

Patients are expected to enrol in a registry and will be followed in the registry in order to better understand the long-term safety and efficacy of Tecartus.

Posology

Tecartus is intended for autologous use only (see section 4.4).

A single dose of Tecartus contains 2×10^6 CAR-positive viable T cells per kg of body weight (range: 1×10^6–2×10^6 cells/kg), or maximum of 2×10^8 CAR-positive viable T cells for patients 100 kg and above in approximately 68 mL dispersion in an infusion bag.

Tecartus is recommended to be infused 3 to 14 days after completion of the lymphodepleting chemotherapy. The availability of the treatment must be confirmed prior to starting the lymphodepleting regimen.

Pre-treatment (lymphodepleting chemotherapy)
- A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m² and fludarabine 30 mg/m² should be administered intravenously on the 5th, 4th, and 3rd day before infusion of Tecartus.

Pre-medication
- To minimise potential acute infusion reactions, it is recommended that patients be pre-medicated with paracetamol 500 to 1,000 mg given orally and diphenhydramine 12.5 to 25 mg intravenous or oral (or equivalent) approximately 1 hour prior to infusion.
- Prophylactic use of systemic corticosteroids is not recommended (see section 4.5).

Monitoring after infusion
- Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurologic events.
- After the first 10 days following the infusion, the patient should be monitored at the physician's discretion.
- Patients should be instructed to remain within proximity (within 2 hours of travel) of a qualified treatment centre for at least 4 weeks following infusion.

Special populations

Elderly
No dose adjustment is required in patients ≥65 years of age.

Patients seropositive for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV)
There is no experience with manufacturing Tecartus for patients with a positive test for HIV, active HBV, or active HCV infection. Therefore, the benefit/risk has not yet been established in this population.

Paediatric population
The safety and efficacy of Tecartus in children and adolescents aged less than 18 years have not yet been established. No data are available.

Method of administration

Tecartus is for intravenous use only.

Tecartus must not be irradiated. Do NOT use a leukodepleting filter.

Precautions to be taken before handling or administering the medicinal product
This medicinal product contains genetically modified human blood cells. Healthcare professionals handling Tecartus should take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases (see section 6.6).

Preparation for infusion
- Verify that the patient's identity (ID) matches the patient identifiers on the Tecartus metal cassette.
- The Tecartus infusion bag must not be removed from the metal cassette if the information on the patient-specific label does not match the intended patient.
- Once the patient ID is confirmed, remove the infusion bag from the metal cassette.
- Check that the patient information on the metal cassette label matches that on the bag label.
- Inspect the infusion bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines for handling of waste of human-derived material (or immediately contact Kite).
- Place the infusion bag inside a second bag.
- Thaw Tecartus at approximately 37 °C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Tecartus should not be washed, spun down, and/or re-suspended in new media prior to infusion. Thawing should take approximately 3 to 5 minutes.
- Once thawed, Tecartus is stable at room temperature (20 °C – 25 °C) for up to 3 hours. However, Tecartus infusion should begin within 30 minutes of thaw completion.

Administration
- For autologous single use only.
- Tocilizumab and emergency equipment should be available prior to infusion and during the monitoring period.
- A leukodepleting filter must not be used.
- Central venous access is recommended for the administration.
- Verify the patient ID again to match the patient identifiers on the Tecartus bag.
- Prime the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection (0.154 mmol sodium per mL) prior to infusion.
- Infuse the entire content of the Tecartus bag within 30 minutes by either gravity or a peristaltic pump.
- Gently agitate the bag during infusion to prevent cell clumping.
- After the entire content of the bag is infused, rinse the tubing at the same infusion rate with sodium chloride 9 mg/mL (0.9%) solution for injection (0.154 mmol sodium per mL) to ensure all the treatment is delivered.

For instructions on the handling, accidental exposure to and disposal of the medicinal product, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Contraindications of the lymphodepleting chemotherapy must be considered.

4.4 Special warnings and precautions for use

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient should be kept for a period of 30 years.

General

Warnings and precautions of lymphodepleting chemotherapy must be considered.

Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurologic events. After the first 10 days following infusion, the patient should be monitored at the physician's discretion.

Counsel patients to remain within the proximity of a qualified treatment centre for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of CRS or neurological adverse reactions occur. Monitoring of vital signs and organ functions should be considered depending on the severity of the reaction.

Reasons to delay treatment

Due to the risks associated with Tecartus treatment, infusion should be delayed if a patient has any of the following conditions:

- Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions, or hypotension) including from preceding chemotherapies.
- Active uncontrolled infection or inflammatory disease.
- Active graft-versus-host disease (GvHD).

In some cases, the treatment may be delayed after administration of the lymphodepleting chemotherapy regimen. If the infusion is delayed for more than 2 weeks after the patient has received the lymphodepleting chemotherapy, lymphodepleting chemotherapy regimen should be administered again (see section 4.2)

Serological testing

Screening for HBV, HCV, and HIV should be performed before collection of cells for manufacturing of Tecartus (see section 4.2).

Blood, organ, tissue and cell donation

Patients treated with Tecartus should not donate blood, organs, tissues, or cells for transplantation.

Active central nervous system (CNS) lymphoma

There is no experience of use of this medicinal product in patients with active CNS lymphoma defined as detectable cerebrospinal fluid malignant cells or brain metastases confirmed by imaging. Therefore, the benefit/risk of Tecartus has not been established in this population.

Concomitant disease

Patients with a history of or active CNS disorder or inadequate renal, hepatic, pulmonary, or cardiac function were excluded from the study. These patients are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention.

Cytokine release syndrome

Nearly all patients experienced some degree of CRS. Severe CRS, which can be life-threatening, was very commonly observed with Tecartus with a median time to onset of 3 days (range: 1 to 13 days). Patients should be closely monitored for signs or symptoms of these events, such as high fever, hypotension, hypoxia, chills, tachycardia and headache (see section 4.8). CRS should be managed at the physician's discretion, based on the patient's clinical presentation and according to the CRS management algorithm provided in Table 1.

Diagnosis of CRS requires excluding alternate causes of systemic inflammatory response, including infection.

Management of cytokine release syndrome associated with Tecartus
At least 1 dose per patient of tocilizumab, an interleukin-6 (IL-6) receptor inhibitor, must be on site and available for administration prior to Tecartus infusion. The qualified treatment centre should have access to an additional dose of tocilizumab within 8 hours of each previous dose.

Treatment algorithms have been developed to ameliorate some of the CRS symptoms experienced by patients on Tecartus. These include the use of tocilizumab or tocilizumab and corticosteroids, as summarised in Table 1. Patients who experience Grade 2 or higher CRS (e.g. hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive-care supportive therapy.

CRS has been known to be associated with end organ dysfunction (e.g., hepatic, renal, cardiac, and pulmonary). In addition, worsening of underlying organ pathologies can occur in the setting of CRS. Patients with medically significant cardiac dysfunction should be managed by standards of critical care and measures such as echocardiography should be considered. In some cases, macrophage activation syndrome (MAS) and haemophagocytic lymphohistiocytosis (HLH) may occur in the setting of CRS.

Evaluation for haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) should be considered in patients with severe or unresponsive CRS.

Tecartus continues to expand and persist following administration of tocilizumab and corticosteroids. Tumour necrosis factor (TNF) antagonists are not recommended for management of Tecartus-associated CRS.

Table 1 CRS grading and management guidance

CRS Grade *(a)*	**Tocilizumab**	**Corticosteroids**
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	If not improving after 24 hours, administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg).	N/A

CRS Grade *(a)*	Tocilizumab	Corticosteroids
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO_2 or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity *(b)*.	Administer tocilizumab *(c)* 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24 hour period; maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS, or if no response to second or subsequent doses of tocilizumab, consider alternative measures for treatment of CRS. If improving, discontinue tocilizumab.	If no improvement within 24 hours after starting tocilizumab, manage as per Grade 3. If improving, taper corticosteroids, and manage as Grade 1.
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO_2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours) until Grade 1, then taper corticosteroids. If improving, manage as Grade 2. If not improving, manage as Grade 4.
Grade 4 Life-threatening symptoms. Requirements for ventilator support or continuous veno-venous haemodialysis or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2	Administer methylprednisolone 1000 mg intravenously per day for 3 days. If improving, taper corticosteroids, and manage as Grade 3. If not improving, consider alternate immunosuppressants.

N/A = not available/not applicable
(a) Lee et al 2014.
(b) Refer to Table 2 for management of neurologic adverse reactions.
(c) Refer to tocilizumab summary of product characteristics for details.

Neurologic adverse reactions

Severe neurologic adverse reactions (encephalopathy, confusional state or delirium, decreased level of consciousness, seizures, aphasia), which could be life-threatening, were very commonly observed in patients treated with Tecartus with a median time to onset of 8 days (range: 1 to 262 days) (see section 4.8).

Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive-care supportive therapy for severe or life-threatening neurologic toxicities. Non-sedating, anti-seizure medicines should be considered as clinically indicated for Grade 2 or higher adverse reactions. Treatment algorithms have been developed to ameliorate the neurologic adverse reactions experienced by patients on Tecartus. These include the use of tocilizumab (if concurrent CRS) and/or corticosteroids for moderate, severe, or life-threatening neurologic adverse reactions as summarised in Table 2.

Table 2 Neurologic adverse reaction grading and management guidance

Grading assessment	Concurrent CRS	No concurrent CRS
Grade 2	Administer tocilizumab as per Table 1 for management Grade 2 CRS. If not improving within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours until the event is Grade 1 or less, then taper corticosteroids. If improving, discontinue tocilizumab. If still not improving, manage as Grade 3.	Administer dexamethasone 10 mg intravenously every 6 hours until the event is Grade 1 or less. If improving, taper corticosteroids
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 3	Administer tocilizumab as per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids. If improving, discontinue tocilizumab and manage as Grade 2. If still not improving, manage as Grade 4.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids. If not improving, manage as Grade 4.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4	Administer tocilizumab as per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days. If improving, then manage as Grade 3. If not improving, consider alternate immunosuppressants.	Administer methylprednisolone 1000 mg intravenously per day for 3 days. If improving, then manage as Grade 3. If not improving, consider alternate immunosuppressants.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

Infections and febrile neutropenia

Severe infections, which could be life-threatening, were very commonly observed with Tecartus (see section 4.8).

Patients should be monitored for signs and symptoms of infection before, during and after infusion and treated appropriately. Prophylactic antibiotics should be administered according to standard institutional guidelines.

Febrile neutropenia has been observed in patients after Tecartus infusion (see section 4.8) and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

In immunosuppressed patients, life-threatening and fatal opportunistic infections including disseminated fungal infections and viral reactivation (e.g., HHV-6 and progressive multifocal leukoencephalopathy) have been reported. The possibility of these infections should be considered in patients with neurologic events and appropriate diagnostic evaluations should be performed.

Viral reactivation

Viral reactivation, e.g. Hepatitis B virus (HBV) reactivation, can occur in patients treated with medicinal products directed against B cells and could result in fulminant hepatitis, hepatic failure, and death.

Prolonged cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Tecartus infusion and should be managed according to standard guidelines. Grade 3 or higher prolonged cytopenias following Tecartus infusion occurred very commonly and included thrombocytopenia, neutropenia, and anaemia (see section 4.8). Patient blood counts should be monitored after Tecartus infusion.

Hypogammaglobulinaemia

B-cell aplasia leading to hypogammaglobulinaemia can occur in patients receiving treatment with Tecartus. Hypogammaglobulinaemia was very commonly observed in patients treated with Tecartus (see section 4.8). Hypogammaglobulinaemia predisposes patients to have infections. Immunoglobulin levels should be monitored after treatment with Tecartus and managed using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement in case of recurrent infections and should be taken according standard guidelines.

Hypersensitivity reactions

Serious hypersensitivity reactions including anaphylaxis, may occur due to DMSO or residual gentamicin in Tecartus.

Secondary malignancies

Patients treated with Tecartus may develop secondary malignancies. Patients should be monitored life-long for secondary malignancies. In the event that a secondary malignancy occurs, the company should be contacted to obtain instructions on patient samples to collect for testing.

Tumour lysis syndrome (TLS)

TLS, which may be severe, has occasionally been observed. To minimise risk of TLS, patients with elevated uric acid or high tumour burden should receive allopurinol, or an alternative prophylaxis, prior to Tecartus infusion. Signs and symptoms of TLS should be monitored, and events managed according to standard guidelines.

Prior stem cell transplantation (GvHD)

It is not recommended that patients who underwent an allogeneic stem cell transplant and suffer from active acute or chronic GvHD receive treatment because of the potential risk of Tecartus worsening GvHD.

Prior treatment with anti-CD19 therapy

Tecartus is not recommended if the patient has relapsed with CD19-negative disease after prior anti-CD19 therapy.

Sodium content

This medicinal product contains 300 mg sodium per infusion, equivalent to 15% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Prophylactic use of systemic corticosteroids may interfere with the activity of Tecartus. Prophylactic use of systemic corticosteroids is therefore not recommended before infusion (see section 4.2).

Administration of corticosteroids as per the toxicity management guidelines does not impact the expansion and persistence of CAR T cells.

Live vaccines

The safety of immunisation with live viral vaccines during or following Tecartus treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Tecartus treatment, and until immune recovery following treatment.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

The pregnancy status of women of childbearing potential must be verified before starting Tecartus treatment.

See the prescribing information for lymphodepleting chemotherapy for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with Tecartus.

Pregnancy

There are no available data with Tecartus use in pregnant women. No reproductive and developmental toxicity animal studies have been conducted with Tecartus to assess whether it can cause foetal harm when administered to a pregnant woman (see section 5.3).

It is not known if Tecartus has the potential to be transferred to the foetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause foetal toxicity, including B-cell lymphocytopenia. Therefore, Tecartus is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised on the potential risks to the foetus. Pregnancy after Tecartus therapy should be discussed with the treating physician.

Assessment of immunoglobulin levels and B-cells in newborn infants of mothers treated with Tecartus should be considered.

Breast-feeding

It is unknown whether Tecartus is excreted in human milk or transferred to the breast-feeding child. Breast-feeding women should be advised of the potential risk to the breast-fed child.

Fertility

No clinical data on the effect of Tecartus on fertility are available. Effects on male and female fertility have not been evaluated in animal studies.

4.7 Effects on ability to drive and use machines

Tecartus has major influence on the ability to drive and use machines.

Due to the potential for neurologic events, including altered mental status or seizures, patients should not drive or operate heavy or potentially dangerous machines until at least 8 weeks after infusion or until resolution of neurologic adverse reactions.

4.8 Undesirable effects

Summary of the safety profile

The safety data described in this section reflect exposure to Tecartus in ZUMA-2, a Phase 2 study in which a total of 82 patients with relapsed/refractory MCL received a single dose of CAR-positive viable T cells (2×10^6 or 0.5×10^6 anti-CD19 CAR T cells/kg) based on a recommended dose which was weight-based.

The most significant and frequently occurring adverse reactions were cytokine release syndrome (91%), infections (56%) and encephalopathy (51%).

Serious adverse reactions occurred in 57% of patients. The most common serious adverse reactions included encephalopathy (26%), infections (28%) and cytokine release syndrome (15%).

Grade 3 or higher adverse reactions were reported in 65% of patients. The most common Grade 3 or higher non-haematological adverse reactions included infections (32%) and encephalopathy (24%). The most common Grade 3 or higher haematological adverse reactions included neutropenia (99%), leukopenia (98%), lymphopenia (96%), thrombocytopenia (65%) and anaemia (56%).

Tabulated list of adverse reactions

Adverse reactions described in this section were identified in patients exposed to Tecartus in ZUMA-2. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3 Adverse drug reactions identified with Tecartus

System Organ Class (SOC)	Frequency	Adverse reactions
Infections and infestations		
	Very common	Unspecified pathogen infections Viral infections Bacterial infections Fungal infections
Blood and lymphatic system disorders		
	Very common	Neutropenia[a] Lymphopenia[a] Leukopenia[a] Anaemia[a] Thrombocytopenia[a] Coagulopathy
Immune system disorders		
	Very common	Cytokine Release Syndrome[b] Hypogammaglobulinaemia
Metabolism and nutrition disorders		
	Very common	Hypophosphataemia[a] Decreased appetite
	Common	Dehydration Hypoalbuminemia[a]

System Organ Class (SOC)	Frequency	Adverse reactions
Psychiatric disorders		
	Very common	Insomnia Delirium Anxiety
Nervous system disorders		
	Very common	Encephalopathy Tremor Headache Aphasia Dizziness Neuropathy
	Common	Ataxia Seizure Increased intracranial pressure
Cardiac disorders		
	Very common	Tachycardias Bradycardias
	Common	Non-ventricular arrhythmias
Vascular disorders		
	Very common	Hypotension Hypertension Thrombosis
	Common	Haemorrhage
Respiratory, thoracic and mediastinal disorders		
	Very common	Cough Pleural effusion Dyspnoea Hypoxia
	Common	Respiratory failure Pulmonary oedema
Gastrointestinal disorders		
	Very common	Constipation Nausea Diarrhoea Oral pain Abdominal pain Vomiting Dysphagia
	Common	Dry mouth
Skin and subcutaneous tissue disorders		
	Very common	Rash
Musculoskeletal and connective tissue disorders		
	Very common	Motor dysfunction Musculoskeletal pain
Renal and urinary disorders		
	Very common	Renal insufficiency Urine output decreased
General disorders and administration site conditions		
	Very common	Fatigue Oedema Pyrexia Pain Chills
Investigations		
	Very common	Alanine aminotransferase increased[a] Aspartate aminotransferase increased[a] Hypokalaemia[a] Hyponatraemia[a] Hypocalcaemia[a] Blood uric acid increased[a]

System Organ Class (SOC)	Frequency	Adverse reactions
Only cytopenias that resulted in (i) new or worsening clinical sequelae or (ii) that required therapy or (iii) adjustment in current therapy are included in Table 3. [a] Frequency based on Grade 3 or higher laboratory parameter. [b] See section Description of selected adverse reactions.		

Description of selected adverse reactions

Cytokine release syndrome
CRS occurred in 91% of patients. Fifteen percent (15%) of patients experienced Grade 3 or higher (severe or life-threatening) CRS. The median time to onset was 3 days (range: 1 to 13 days) and the median duration was 10 days (range: 1 to 50 days). All patients (100%) recovered from CRS.

The most common signs or symptoms associated with CRS among the patients who experienced CRS included pyrexia (99%), hypotension (60%), hypoxia (37%), chills (33%), tachycardia (27%), headache (24%), fatigue (16%), nausea (13%), alanine aminotransferase increased (13%), aspartate aminotransferase increased (12%), diarrhoea (11%), and sinus tachycardia (11%). Serious adverse reactions that may be associated with CRS included hypotension, pyrexia, hypoxia, acute kidney injury, and tachycardia. See section 4.4 for monitoring and management guidance.

Neurologic events and adverse reactions
Neurologic adverse reactions occurred in 68% of patients. Thirty-three percent (33%) of patients experienced Grade 3 or higher (severe or life-threatening) adverse reactions. The median time to onset was 8 days (range: 1 to 262 days). Neurologic events resolved for 47 out of 56 patients with a median duration of 13 days (range: 1 to 567 days). Three patients had ongoing neurologic events at the time of death, including one patient with the reported event of serious encephalopathy and another patient with the reported event of serious confusional state. The remaining unresolved neurologic events were Grade 2. Eighty-five percent of all treated patients experienced the first CRS or neurological event within the first 7 days after Tecartus infusion.

The most common neurologic adverse reactions included encephalopathy (51%), tremor (38%), aphasia (20%), and delirium (18%). Serious adverse reactions including encephalopathy (26%), aphasia (6%) and seizure (2%) have been reported in patients administered with Tecartus. Serious cases of cerebral oedema which may become fatal have occurred in patients treated with Tecartus. See section 4.4 for monitoring and management guidance.

Febrile neutropenia and infections
Febrile neutropenia was observed in 6% of patients after Tecartus infusion. Infections occurred in 56% of patients in ZUMA-2. Grade 3 or higher (severe, life-threatening or fatal) infections occurred in 32% of patients including unspecified pathogen, bacterial, and viral infections in 26%, 6%, and 4% of patients respectively. See section 4.4 for monitoring and management guidance.

Prolonged cytopenias
Cytopenias are very common following prior lymphodepleting chemotherapy and Tecartus therapy.

Prolonged (present on or beyond Day 30 or with an onset at Day 30 or beyond) Grade 3 or higher cytopenias occurred in 55% of patients and included thrombocytopenia (38%), neutropenia (37%), and anaemia (17%). See section 4.4 for management guidance.

Hypogammaglobulinaemia
In ZUMA-2, hypogammaglobulinaemia occurred in 16% of patients. Grade 3 or higher hypogammaglobulinemia occurred in 1% of patients. See section 4.4 for management guidance.

Immunogenicity

The immunogenicity of Tecartus has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the

anti-CD19 CAR. To date, no anti-CD19 CAR T-cell antibody immunogenicity has been observed. Based on an initial screening assay, 17 patients tested positive for antibodies; however, a confirmatory orthogonal cell-based assay demonstrated that all 17 patients were antibody negative at all time points tested. There is no evidence that the kinetics of initial expansion, CAR T-cell function and persistence of Tecartus, or the safety or effectiveness of Tecartus, was altered in these patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There are no data regarding the signs of overdose with Tecartus.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: not yet assigned

Mechanism of action

Tecartus, a CD19-directed genetically modified autologous T-cell immunotherapy, binds to CD19 expressing cancer cells and normal B cells. Following anti-CD19 CAR T-cell engagement with CD19 expressing target cells, the CD28 co-stimulatory domain and CD3-zeta signalling domain activate downstream signalling cascades that lead to T-cell activation, proliferation, acquisition of effector functions and secretion of inflammatory cytokines and chemokines. This sequence of events leads to killing of CD19-expressing cells.

Pharmacodynamic effects

In ZUMA-2, after Tecartus infusion, pharmacodynamic responses were evaluated over a 4-week interval by measuring transient elevation of cytokines, chemokines, and other molecules in blood. Levels of cytokines and chemokines such as IL-6, IL-8, IL-10, IL-15, TNF-α, interferon-gamma (IFN-γ) and IL-2 receptor alpha were analysed. Peak elevation was generally observed between 4 and 8 days after infusion and levels generally returned to baseline within 28 days.

Due to the on target, off-tumour effect of Tecartus a period of B-cell aplasia is expected following treatment.

Translational analyses performed to identify associations between cytokine levels and incidence of CRS or neurologic events showed that higher levels (peak and AUC at 1 month) of multiple serum analytes were associated with Grade 3 or higher neurologic adverse reactions and Grade 3 or higher CRS.

Clinical efficacy and safety

Relapsed or refractory MCL: ZUMA-2
The efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL who had previously received anthracycline or bendamustine-containing chemotherapy, an anti CD20 antibody, and a Bruton's tyrosine kinase inhibitor (BTKi) (ibrutinib or acalabrutinib), was evaluated in a phase 2 single-arm, open-label, multicenter trial. Eligible patients also had disease progression after last regimen or refractory disease to the most recent therapy. Patients with active or serious infections, prior allogeneic haematopoietic stem cell transplantation (HSCT), detectable cerebrospinal fluid

malignant cells or brain metastases, and any history of central nervous system lymphoma or CNS disorders were ineligible. In total, 74 patients were enrolled (*i.e.* leukapheresed) and 68 patients were treated with Tecartus. Three patients did not receive Tecartus due to manufacturing failure. Two other patients were not treated due to progressive disease (death) following leukapheresis. One patient was not treated with Tecartus after receiving lymphodepleting chemotherapy due to ongoing active atrial fibrillation. ITT was defined as all patients who underwent leukapheresis. A summary of the patient baseline characteristics is provided in Table 4.

Table 4 Summary of baseline characteristics for ZUMA-2

Category	**All leukapheresed (ITT) (N=74)**
Age (years)	
Median (min, max)	65 (38, 79)
≥ 65	58%
Male gender	84%
Median number of prior therapies (min, max)	3 (1; 5)
Relapsed/refractory subgroup	
Relapsed after auto-SCT	42%
Refractory to last MCL therapy	39%
Relapsed after last MCL therapy	19%
Patients with disease stage IV	86%
Patients with bone marrow involvement	51%
Morphological characteristic	
Classical MCL	54%
Blastoid MCL	26%
Other	1%
Unknown	19%
Received bridging therapy	
Yes	38%
No	62%
Ki-67 IHC by central laboratory	
N	49
Median	65%
Auto-SCT, autologous stem cell transplant; IHC, immunohistochemistry; Max, maximum; MCL, mantle cell lymphoma; Min, minimum;	

Tecartus was administered to patients as a single intravenous infusion at a target dose of 2×10^6 anti-CD19 CAR T cells/kg (maximum permitted dose: 2×10^8 cells) after lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously, both given on the 5th, 4th, and 3rd day before treatment. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was permitted to control disease burden.

For patients treated with Tecartus, the median time from leukapheresis to product release was 13 days (range: 9 to 20 days) and the median time from leukapheresis to Tecartus infusion was 27 days (range: 19 to 74 days, with the exception of one outlier of 134 days). The median dose was 2.0×10^6 anti-CD19 CAR T cells/kg. All patients received Tecartus infusion on day 0 and were hospitalized until day 7 at the minimum.

The primary endpoint was objective response rate (ORR) as determined by Lugano 2014 criteria by an independent review committee. Secondary endpoints included duration of response (DOR), overall survival (OS), progression free survival (PFS) and severity of adverse events.

An analysis set was defined a priori which consisted of the first 60 patients treated with Tecartus who were evaluated for response 6 months after the Week 4 disease assessment after Tecartus infusion. In this analysis set of 60 patients the ORR was 93% with a CR rate of 67%. The ORR was significantly higher than the prespecified historical control rate of 25% at a 1-sided significance level of 0.025 ($p < 0.0001$). Results in the ITT set are shown in Table 5.

Table 5 Summary of efficacy results for ZUMA-2

Category	**All leukapheresed [a](ITT) (N = 74)**
Objective response rate (ORR), n (%) [95% CI]	**62 (84%)** [73.4, 91.3]
CR n (%) [95% CI]	44 (59%) [47.4, 70.7]
PR n (%) [95% CI]	18 (24%) [15.1, 35.7]
Duration of response (DOR)[b]	
Median in months [95% CI]	NR [10.4, NE]
Range [c] in months	0.0+, 35.0+
Ongoing responses, CR+PR, CR, n (%) [d]	32 (43%), 30 (41%)
Progression free survival	
Median, months [95% CI]	16.2 [9.9, NE]
Overall survival	
Median, months [95% CI]	NR [24.6, NE]
6 month OS (%) [95% CI]	83.6 [72.9, 90.3]
12 month OS (%) [95% CI]	76.6 [65.1, 84.8]
24 month OS (%) [95% CI]	66.5 [52.8, 77.1]
Median Follow-up in months (min, max)	16.8 [7.2, 37.6]

CI, confidence interval; CR, complete remission; ITT, intent to treat; NE, not estimable; NR, not reached; OS, overall survival; PR, partial remission.

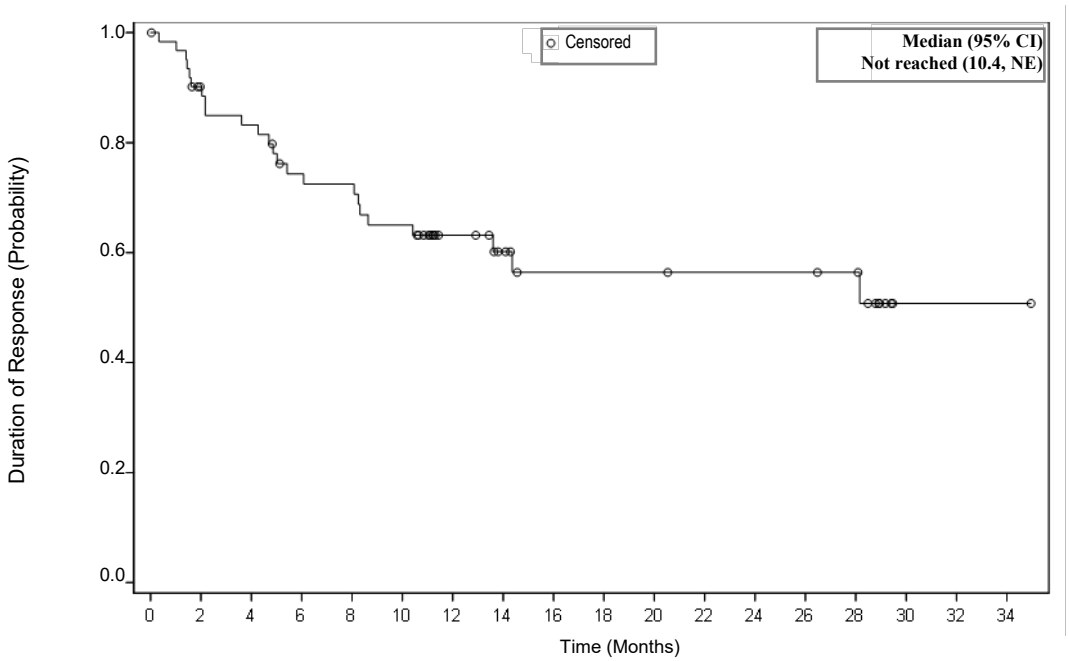
a Of the 74 patients that were enrolled (*i.e.* leukapheresed), 69 patients received lymphodepleting chemotherapy, and 68 patients received Tecartus.

b Among all responders. DOR is measured from the date of first objective response to the date of progression or death.

c A + sign indicates a censored value.

d At the data cutoff date. Percentages are calculated using the total number of patients in the analysis set as the denominator.

Figure 1 Kaplan Meier DOR in the intent to treat set



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Tecartus in all subsets of the paediatric population in treatment of mantle cell lymphoma (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme.
This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Following infusion of Tecartus, anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by 3 months. Peak levels of anti-CD19 CAR T cells occurred within the first 7 to 15 days after the infusion.

The number of anti-CD19 CAR T cells in blood was associated with objective response (CR or PR) (Table 6).

Table 6 Kinetic parameters of autologous anti-CD19-transduced CD3+ cells in ZUMA-2

Number of anti-CD19 CAR T cell	**Responding patients (CR or PR) (N=63)**	**Non-responding patients (N=5)**	**P-Value**
Peak (cells/µL) Median [min; max], n	97.52 [0.24, 2589.47], 62	0.39 [0.16, 22.02], 5	0.0020
$AUC_{0–28}$ (cells/µL·days) Median [min; max], n	1386.28 [3.83 to 2.77×10^4], 62	5.51 [1.81, 293.86], 5	0.0013

P-value is calculated by Wilcoxon test

Median peak anti-CD19 CAR T-cell values were 74.08 cells/µL in patients ≥65 years of age (n=39) and 112.45 cells/µL in patients <65 years of age (n=28). Median anti-CD19 CAR T-cell AUC values were 876.48 cells/µL·day in patients ≥65 years of age and 1640.21 cells/µL·day in patients <65 years of age.

Gender had no significant impact on $AUC_{Day\ 0–28}$ and C_{max} of Tecartus.

Studies of Tecartus in patients with hepatic and renal impairment were not conducted.

5.3 Preclinical safety data

Tecartus comprises engineered human T cells; therefore, there are no representative *in vitro* assays, *ex vivo* models, or *in vivo* models that can accurately address the toxicological characteristics of the human product. Hence, traditional toxicology studies used for medicinal product development were not performed.

No carcinogenicity or genotoxicity studies have been conducted.

No studies have been conducted to evaluate the effects of this treatment on fertility, reproduction, and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cryostor CS10
Sodium chloride
Human albumin

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Tecartus is stable for 1 year when stored frozen in the vapour phase of liquid nitrogen (≤ − 150°C).

Tecartus is stable at room temperature (20 °C to 25 °C) for up to 3 hours after thawing. However, Tecartus infusion should begin within 30 minutes of thaw completion and the total infusion time should not exceed 30 min. Thawed product should not be refrozen.

6.4 Special precautions for storage

Tecartus must be stored in the vapour phase of liquid nitrogen (≤ − 150 °C) and must remain frozen until the patient is ready for treatment to ensure viable live autologous cells are available for patient administration.

For storage conditions after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Ethylene-vinyl acetate cryostorage bag with sealed addition tube and two available spike ports, containing approximately 68 mL of cell dispersion.

One cryostorage bag is individually packed in a shipping metal cassette.

6.6 Special precautions for disposal and other handling

Irradiation could lead to inactivation of the product.

Precautions to be taken for the transport and disposal of the medicinal product

Tecartus should be transported within the facility in closed, break-proof, leak-proof containers.

Tecartus contains genetically modified human blood cells. Local guidelines on handling of waste of human-derived material should be followed for unused medicinal products or waste material. All material that has been in contact with Tecartus (solid and liquid waste) should be handled and disposed of in accordance with local guidelines on handling of waste of human-derived material.

Accidental exposure to Tecartus must be avoided. Local guidelines on handling of human-derived material should be followed in case of accidental exposure, which may include washing of the contaminated skin and removal of contaminated clothes. Work surfaces and materials which have potentially been in contact with Tecartus must be decontaminated with appropriate disinfectant.

7. MARKETING AUTHORISATION HOLDER

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1492/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance

Kite Pharma, Inc.
2355 Utah Avenue
El Segundo
California
CA 90245
United States

Name and address of the manufacturer(s) responsible for batch release

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Key elements:

Availability of tocilizumab and site qualification

To minimise the risks associated with the treatment of Tecartus, the MAH must ensure that hospitals and their associated centres that dispense Tecartus are specially qualified in accordance with the agreed controlled distribution program.

The MAH must ensure on-site, immediate access to at least 1 dose of tocilizumab for each patient as cytokine release syndrome (CRS) management medication prior to treating patients. Hospitals and their associated centres should have access to an additional dose of tocilizumab within 8 hours of each previous dose.

Tecartus will only be supplied to hospitals and associated centres that are qualified and only if the healthcare professionals (HCP) involved in the treatment of a patient have completed the educational program.

Educational program – Prior to the launch of Tecartus in each Member State the MAH must agree the content and format of the educational materials with the National Competent Authority.

HCP Educational program

The MAH shall ensure that in each Member State where Tecartus is marketed, all HCPs who are expected to prescribe, dispense, and administer Tecartus shall be provided with a guidance document to:

- provide information about the safety and efficacy long-term follow up study and the importance of contributing to such a study
- facilitate identification of CRS and serious neurologic adverse reactions
- facilitate management of the CRS and serious neurologic adverse reactions
- ensure adequate monitoring of CRS and serious neurologic adverse reactions
- facilitate provision of all relevant information to patients
- ensure that adverse reactions are adequately and appropriately reported
- ensure that detailed instructions about the thawing procedure are provided
- before treating a patient, ensure that at least 1 dose of tocilizumab for each patient is available on site. The qualified treatment centre must have access to additional doses of tocilizumab within 8 hours

Patient Educational program

To inform and explain to patients:

- the risks of CRS and serious neurologic adverse reactions, associated with Tecartus
- the need to report the symptoms to their treating doctor immediately
- the need to remain in the proximity of the location where Tecartus was received for at least 4 weeks following Tecartus infusion
- the need to carry the patient alert card at all times

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to further characterise the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory Mantle cell Lymphoma (MCL) the MAH shall conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol.	Interim reports to be submitted in accordance with the RMP. 30 June 2042

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14a(4) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL and the Benefit/Risk balance in the female, elderly and severely diseased patients, the MAH shall submit the results of a prospective study investigating efficacy and safety based on data from the same registry used to characterise the long-term efficacy and safety of Tecartus, according to an agreed protocol.	30 September 2025
In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL the MAH shall submit the 24 months follow-up data from all treated patients in cohort 1 of the pivotal study ZUMA-2.	31 March 2022

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

METAL CASSETTE

1. NAME OF THE MEDICINAL PRODUCT

Tecartus 0.4 – 2 × 10^8 cells dispersion for infusion
autologous anti-CD19-transduced CD3+ cells (CAR+ viable T cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous human T cells transduced with retroviral vector encoding an anti-CD19 chimeric antigen receptor (CAR) with a target dose of 2 × 10^6 anti-CD19 CAR positive viable T cells/kg.

3. LIST OF EXCIPIENTS

Excipients: Cryostor CS10, human albumin, sodium chloride.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
One sterile infusion bag.
Contents: approximately 68 mL of cell dispersion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Do not irradiate.
For intravenous use only.
Gently mix the contents of the bag while thawing.
Do NOT use a leukodepleting filter.
STOP confirm patient ID prior to infusion.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store frozen in vapour phase of liquid nitrogen ≤ − 150 °C.
Do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Contains genetically-modified cells.
Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1492/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot:
Kite Patient ID:
Additional Patient ID:
Patient Name:
Patient DOB:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INFUSION BAG

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Tecartus 0.4 – 2 × 10^8 cells dispersion for infusion
autologous anti-CD19-transduced CD3+ cells (CAR+ viable T cells)
For intravenous use only.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot:
Kite Patient ID:
Additional Patient ID:
Patient Name:
Patient DOB:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Contents: approximately 68 mL of cell dispersion.

6. OTHER

For autologous use only.
Verify patient ID.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Tecartus 0.4 – 2 × 10^8 cells dispersion for infusion
autologous anti-CD19-transduced CD3+ cells (CAR+ viable T cells)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will give you a Patient Alert Card. Read it carefully and follow the instructions on it.
- Always show the Patient Alert Card to the doctor or nurse when you see them or if you go to hospital.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tecartus is and what it is used for

Tecartus is a gene therapy medicine used for treating mantle cell lymphoma in adults. It is used when other medicines have stopped working for you (relapsed or refractory mantle cell lymphoma). The medicine is made specially for you from your own white blood cells that have been modified and are known as autologous anti-CD19-transduced CD3+ cells.

Mantle cell lymphoma is a cancer of a part of the immune system (the body's defences). It affects a type of white blood cell called B-lymphocytes. In mantle cell lymphoma, B-lymphocytes grow in an uncontrolled way and build up in the lymph tissue, bone marrow or blood.

How Tecartus works
The white blood cells are taken from your blood and are genetically modified so that they can target the cancer cells in your body. When Tecartus is infused into your blood, the modified white blood cells will kill the cancer cells.

2. What you need to know before you are given Tecartus

You are not to be given Tecartus
- if you are allergic to any of the ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.
- if you can't receive the medicine to reduce the number of white blood cells in your blood (*lymphodepleting chemotherapy*) (see also section 3, How Tecartus is given).

Warnings and precautions
Tecartus is made from your own white blood cells and should only be given to you (*autologous use*).

Tests and checks
Before you are given Tecartus your doctor will:
- Check your lungs, heart, kidney and blood pressure.
- Look for signs of infection or inflammation; and decide whether you need to be treated before you are given Tecartus.
- Check if your cancer is getting worse.
- Look for signs of graft-versus-host disease that can happen after a transplant. This happens when transplanted cells attack your body, causing symptoms such as rash, nausea, vomiting, diarrhoea and bloody stools.
- Check your blood for uric acid and for how many cancer cells there are in your blood. This will show if you are likely to develop a condition called *tumour lysis syndrome.* You may be given medicines to help prevent the condition.
- Check for hepatitis B, hepatitis C or HIV infection.
- Check if you had a vaccination in the previous 6 weeks or are planning to have one in the next few months.
- Check if you have previously received a treatment that attaches to the protein called CD19.

In some cases, it might not be possible to go ahead with the planned treatment with Tecartus. If Tecartus infusion is delayed for more than 2 weeks after you have received lymphodepleting chemotherapy you may have to receive more chemotherapy (see also section 3, How Tecartus is given).

After you have been given Tecartus
Tell your doctor or nurse immediately or get emergency help right away if you have any of the following:
- Chills, extreme tiredness, weakness, dizziness, headache, cough, shortness of breath, rapid or irregular heartbeat, severe nausea, vomiting, or diarrhoea which may be symptoms of a condition known as *cytokine release syndrome.* Take your temperature twice a day for 3 to 4 weeks after treatment with Tecartus. If your temperature is high, see your doctor immediately.
- Fits, shaking, or difficulty speaking or slurred speech, loss of consciousness or decreased level of consciousness, confusion and disorientation, loss of balance or coordination.
- Fever (e.g. temperature above 38°C), which may be a symptom of an infection.
- Extreme tiredness, weakness and shortness of breath, which may be symptoms of a lack of red blood cells.
- Bleeding or bruising more easily, which may be symptoms of low levels of cells in the blood known as platelets.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse.

Your doctor will regularly check your blood counts as the number of blood cells and other blood components may decrease.

You will be asked to enrol in a registry for at least 15 years in order to better understand the long-term effects of Tecartus.

Do not donate blood, organs, tissues, or cells for transplants.

Children and adolescents
Tecartus should not be used in children and adolescents below 18 years of age.

Other medicines and Tecartus
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

Before you are given Tecartus tell your doctor or nurse if you are taking any medicines that weaken your immune system such as corticosteroids, since these medicines may interfere with the effect of Tecartus.

In particular, you must not be given certain vaccines called live vaccines:
- In the 6 weeks before you are given the short course of lymphodepleting chemotherapy to prepare your body for the Tecartus cells.
- During Tecartus treatment.
- After treatment while the immune system is recovering.

Talk to your doctor if you need to have any vaccinations.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine. This is because the effects of Tecartus in pregnant or breast-feeding women are not known, and it may harm your unborn baby or your breast-fed child.
- If you are pregnant or think you may be pregnant after treatment with Tecartus, talk to your doctor immediately.
- You will be given a pregnancy test before treatment starts. Tecartus should only be given if the results show you are not pregnant.

Discuss pregnancy with your doctor if you have received Tecartus.

Driving and using machines
Tecartus can cause problems such as altered or decreased consciousness, confusion and seizures (fits) in the 8 weeks after it is given.

Do not drive, use machines, or take part in activities that need you to be alert for at least 8 weeks after your Tecartus treatment or until your doctor tells you that you have completely recovered.

Tecartus contains sodium, dimethylsulfoxide (DMSO) and gentamicin
This medicine contains 300 mg sodium (main component of cooking/table salt) in each infusion. This is equivalent to 15% of the recommended maximum daily dietary intake of sodium for an adult. It also contains DMSO and gentamicin which may cause severe hypersensitivity reactions.

3. How Tecartus is given

Tecartus will always be given to you by a healthcare professional.

- Since Tecartus is made from your own white blood cells, your cells will be collected from you to prepare your medicine. Your doctor will take some of your blood using a catheter placed in your vein (a procedure call *leukapheresis*). Some of your white blood cells are separated from your blood and the rest of your blood is returned to your vein. This can take 3 to 6 hours and may need to be repeated.
- Your white blood cells are sent away to a manufacturing center to make your Tecartus. It usually takes about 2 to 3 weeks to make Tecartus but the time may vary.

Medicines given before Tecartus treatment
A few days before you receive Tecartus, you will be given lymphodepleting chemotherapy, which will allow the modified white blood cells in Tecartus to multiply in your body when the medicine is given to you.

During the 30 to 60 minutes before you are given Tecartus you may be given other medicines. This is to help prevent infusion reactions and fever. These other medicines may include:
- Paracetamol.
- An antihistamine such as diphenhydramine.

How you are given Tecartus
Tecartus will always be given to you by a doctor in a qualified treatment centre.

- Tecartus is given in a single dose.
- Your doctor or nurse will give you a single infusion of Tecartus through a catheter placed into your vein (*intravenous infusion*) over about 30 minutes.
- Tecartus is the genetically modified version of your white blood cells. Your healthcare professional handling the treatment will therefore take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases and will follow local guidelines on handling of waste of human-derived material to clean up or dispose of any material that has been in contact with it.

After you are given Tecartus
- You should stay close to the hospital where you were treated for at least 4 weeks after Tecartus treatment. Your doctor will recommend that you return to the hospital daily for at least 10 days or that you stay at the hospital as an in-patient for the first 10 days after Tecartus treatment. This is so your doctor can check if your treatment is working and help you if you have any side effects.

If you miss any appointments, call your doctor or your treatment centre as soon as possible to reschedule your appointment.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Do not try to treat your side effects on your own.

Tecartus can cause side effects that may be serious or life-threatening. **Get urgent medical attention** if you get any of the following side effects after the Tecartus infusion.

Very common: may affect more than 1 in 10 people
- Fever, chills, reduced blood pressure which may cause symptoms such as dizziness, lightheadedness, fluid in the lungs, which may be severe and can be fatal (all symptoms of a condition called *cytokine release syndrome*).
- Loss of consciousness or decreased level of consciousness, confusion or memory loss due to disturbances of brain function, difficulty speaking or slurred speech, involuntary shaking (*tremor*), fits (*seizures*), sudden confusion with agitation, disorientation, hallucination or irritability (*delirium*).
- Fever, chills, which may be signs of an infection.

Other possible side effects
Other side effects are listed below. If these side effects become severe or serious, tell your doctor immediately.

Very common: may affect more than 1 in 10 people
- Abnormally low number of white blood cells, which may increase your risk of infection.
- Low number of cells that help clot the blood *(thrombocytopenia)*, alteration of the blood's ability to form clots: symptoms can include excessive or prolonged bleeding or bruising.
- High blood pressure.
- Decrease in the number of red blood cells (cells that carry oxygen): symptoms can include extreme tiredness with a loss of energy.

– Extreme tiredness.
– Fast or slow heartbeat.
– Decrease of oxygen reaching body tissues: symptoms can include changes to the colour of your skin, confusion, rapid breathing.
– Shortness of breath, cough.
– Nausea, constipation, diarrhoea, abdominal pain, vomiting, difficulty swallowing.
– Muscle pain, joint pain, bone pain, pain in the extremities of the body.
– Lack of energy or strength, muscular weakness, difficulty moving, muscle spasm.
– Headache.
– Kidney problems causing your body to hold onto fluid, build-up of fluids in tissue *(oedema)* which can lead to weight gain and difficulty in breathing, decrease output of urine.
– High levels of uric acid seen in blood tests.
– Low levels of sodium, phosphate, potassium or calcium seen in blood tests.
– Decreased appetite, sore mouth.
– Difficulty sleeping, anxiety.
– Swelling in the limbs, fluid around the lungs *(pleural effusion)*.
– Skin rash.
– Low levels of immunoglobulins seen in blood test, which may lead to infections.
– Increase in liver enzymes seen in blood tests.
– Blood clots: symptoms can include pain in the chest or upper back, difficulty breathing, coughing up blood or cramping pain, swelling in a single leg, warm and darkened skin around the painful area.
– Nerve pain.

Common: may affect up to 1 in 10 people
– Low levels of albumin seen in blood tests.
– Excessive bleeding.
– Irregular heartbeat *(arrhythmia)*.
– Loss of control of body movements.
– Dry mouth, dehydration.
– Breathlessness *(respiratory failure)*.
– Difficulty breathing which makes you unable to speak in full sentence, cough due to fluid in the lungs.
– Increase of the pressure inside your skull.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Tecartus

The following information is intended for doctors only.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the container label and infusion bag after EXP.

Store frozen in vapour phase of liquid nitrogen ≤ − 150 °C until thawed for use.
Do not refreeze.

This medicine contains genetically modified human blood cells. Local guidelines on handling of waste of human-derived material should be followed for unused medicinal product or waste material. As this

medicine will be given by qualified healthcare professionals, they are responsible for the correct disposal of the product. These measures will help protect the environment.

6. Contents of the pack and other information

What Tecartus contains
The active substance is autologous anti-CD19-transduced CD3+ cells. Each patient-specific single infusion bag contains a dispersion of anti-CD19 CAR T cells in approximately 68 mL for a target dose of 2×10^6 anti-CD19 CAR-positive viable T cells/kg.
The other ingredients (excipients) are: Cryostor CS10, sodium chloride, human albumin. See section 2 "Tecartus contains sodium".

What Tecartus looks like and contents of the pack
Tecartus is a clear to opaque, white to red dispersion for infusion, supplied in an infusion bag individually packed in a metal cassette. A single infusion bag contains approximately 68 mL of cell dispersion.

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The Netherlands

Manufacturer
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

This medicine has been given ‘conditional approval’.
This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

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The following information is intended for healthcare professionals only:

It is important that you read the entire content of this procedure prior to administering Tecartus.

Precautions to be taken before handling or administering the medicinal product

- Tecartus contains genetically-modified cells. Local guidelines on handling of human-derived material applicable for such products should be followed.
- Tecartus should be transported within the facility in closed, break-proof, leak-proof containers.
- Tecartus is prepared from autologous blood of the patient collected by leukapheresis. Patient leukapheresis material and Tecartus may carry a risk of transmitting infectious viruses to healthcare professionals (HCP) handling the product. Accordingly, HCP should employ appropriate precautions (wearing gloves and glasses) when handling leukapheresis material or Tecartus to avoid potential transmission of infectious diseases.

Preparation for infusion

- Verify that the patient's identity (ID) matches the patient identifiers on the Tecartus metal cassette.
- The Tecartus infusion bag must not be removed from the metal cassette if the information on the patient-specific label does not match the intended patient.
- Once the patient's ID is confirmed, remove the infusion bag from the metal cassette.
- Check that the patient information on the metal cassette label matches that on the bag label.
- Inspect the infusion bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines for handling of waste of human-derived material (or immediately contact Kite).
- Place the infusion bag inside a second bag.
- Thaw Tecartus at approximately 37 °C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Tecartus should not be washed, spun down, and/or re-suspended in new media prior to infusion. Thawing should take approximately 3 to 5 minutes.
- Once thawed, Tecartus is stable at room temperature (20 °C – 25 °C) for up to 3 hours. However, the infusion should begin within 30 minutes of thaw completion.

Do NOT use a leukodepleting filter.

Administration

- The medicine must be administered in a qualified treatment centre by a physician(s) with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with Tecartus.
- Ensure that at least 1 dose of tocilizumab per patient and emergency equipment are available prior to infusion and during the recovery period. Hospitals and associated centres should have access to an additional dose of tocilizumab within 8 hours of each previous dose.
- The patient's identity should be matched with the patient identifiers on the infusion bag.
- Tecartus is for autologous use only.
- Tecartus should be administered as an intravenous infusion using latex-free intravenous tubing without a leukocyte depleting filter within 30 minutes by either gravity or a peristaltic pump.
- Gently agitate the bag during infusion to prevent cell clumping. All contents of the infusion bag should be infused.
- Sterile sodium chloride 9 mg/mL (0.9%) (0.154 mmol sodium per mL) solution for injection should be used to prime the tubing prior to infusion as well as rinse it afterwards. When the full volume of Tecartus has been infused, the infusion bag should be rinsed with 10 to 30 mL sodium chloride 9 mg/mL (0.9%) solution for injection by back priming to ensure as many cells as possible are infused into the patient.

Disposal of Tecartus

- Any unused medicinal product or waste material that has been in contact with Tecartus (solid and liquid waste) should be handled and disposed of in accordance with local guidelines on handling of waste of human-derived material. Work surfaces and material which have potentially been in contact with Tecartus must be decontaminated with appropriate disinfectant.

Accidental exposure

- Accidental exposure to Tecartus must be avoided. Local guidelines on handling of human-derived material should be followed in case of accidental exposure, which may include washing of the contaminated skin, removal of contaminated clothes.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.